UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte BETH P. GOLDSTEIN, MICHAEL W. CLIMO, RICHARD P. NOVICK, and GORDON L. ARCHER

Appeal 2007-1816
Application 09/120,030
Technology Center 1600

DECIDED: October 31, 2007

Before TONI R. SCHEINER, DEMETRA J. MILLS, and NANCY J. LINCK, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL

Appellants appeal under 35 U.S.C. § 134 from a Final Rejection of claims 4, 5, 32, 44-51, 56-59, and 61-66[1] as obvious over the prior art. We have jurisdiction under 35 U.S.C. § 6(b).

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[1] Claims 28 and 35 are also pending but have been withdrawn from consideration.

BACKGROUND

"Lysostaphin is an enzyme, first identified in *Staphylococcus simulans* . . . which has antimicrobial activity by virtue of its proteolytic activity on glycine-containing bridges in the cell wall peptidoglycan of bacteria" (Spec. 1: 36 to 2: 2). "*In vitro*, lysostaphin is particularly active against *Stapylococcus aureus*, . . . although activity against other species of staphylococci has been demonstrated" (*id.* at 2: 3-6).

The present invention "pertains to the administration of lysostaphin for the purpose of treatment of staphylococcus infection in . . . humans" (*id.* at 1: 18-20).

STATEMENT OF THE CASE

Claims 4, 5, 32, 44-51, 57, and 61-66 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Zygmunt,[2] Goldberg,[3] Stark,[4] and Oldham.[5]

Claims 32, 46, 47, 50, 51, 56, 58, and 59 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Zygmunt, Goldberg, Stark, Oldham, and Dixon.[6]

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[2] Walter A. Zygmunt & Peter A. Tavormina, *Lysostaphin: Model for a Specific Enzymatic Approach to Infectious Disease*, *in* PROGRESS IN DRUG DESIGN, Vol. 16, 309-332 (Ernst Jucker ed., 1972).

[3] Leonard M. Goldberg et al., *Studies in Experimental Staphylococcal Endocarditis in Dogs*, Antimicrobial Agents and Chemotherapy 45-52 (1967).

[4] F.R. Stark et al., *Systemic Lysostaphin in Man - Apparent Antimicrobial Activity in a Neutropenic Patient*, 291 New England Journal of Medicine 239-240 (1974).

[5] Elizabeth R. Oldaham and Michael J. Daley, *Lysostaphin: Use of a Recombinant Bactericidal Enzyme as a Mastitis Therapeutic*, 74 Journal of Dairy Science 4175-4182 (1991).

[6] Richard E. Dixon et al., *Lysostaphin: An Enzymatic Approach to Staphylococcal Disease*, 41 Yale Journal of Biology and Medicine 62-68

Claims 4, 32, 44, and 61 are representative of the subject matter on appeal and read as follows:

> 4. A method of treating an established staphylococcal infection of at least one organ or tissue selected from the group consisting of heart valve, blood, kidney, lung, bone and meninges, comprising systemically administering to a human suffering from at least one of said infections an effective amount of at least one recombinantly produced lysostaphin analogue;
>
> wherein multiple doses of the lysostaphin analogue are administered and wherein the amount of lysostaphin analogue(s) administered [is] from 0.5 to 30 mg/kg/day.
>
> 32. The method of Claim 4, further comprising administering a second antimicrobial agent selected from the group consisting of a rifamycin, a glycopeptide and combinations thereof.
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> 44. The method of Claim 4, wherein the amount of lysostaphin analogue(s) administered is no more than 25 mg/kg/day.
>
> 61. The method of claim 4, wherein the infection is cleared from the at least one organ or tissue.

According to the Specification, a "lysostaphin analogue" is defined as "[a]ny enzyme, including lysostaphin (wild type), any lysostaphin mutant or variant, any recombinant, or related enzyme that retains the proteolytic ability, *in vitro* and *in vivo*, of proteolytic attack against glycine-containing bridges in the cell wall peptidoglycan of staphylococci" (Spec. 6: 15-20).

(1968).

FINDINGS OF FACT[7]

Goldberg

1. Goldberg describes a study wherein thirteen dogs infected with experimental acute staphylococcal endocarditis were treated with lysostaphin "administered intravenously in doses of 5 to 50 mg/kg at intervals of 1 to 24 hr. Treatment courses consisted of 1 to 23 injections over periods of 5 hr to 6.5 days" (Goldberg Abstract).

2. All thirteen dogs in Goldberg's study improved clinically after initial therapy. Three experiments were terminated while the dogs were improving, five dogs became clinically well, and five relapsed (Goldberg Abstract). "One relapsed dog [ ] received only a single 50 mg/kg dose, and three other relapsed dogs [ ] received the smallest individual doses in the series of 13 dogs" (*id.* at 48, col. 1). The fifth dog that relapsed did so after a surgical accident (*id.*).

3. "Regardless of the size of the dose, [lysostaphin] therapy resulted in a [substantial] decrease in the number of staphylococci circulating in the blood" and "[q]uantitative culture of tissues showed that lysostaphin treatment resulted in decreased numbers of staphylococci in lung, liver, spleen, kidney, and aortic and mitral valves[;] [h]eart valves were the most easily sterilized tissue" (Goldberg Abstract).

4. "Adverse reactions to lysostaphin were not observed" (Goldberg Abstract).

5. "[L]ysostaphin's selective action against *S. aureus* and no other bacteria would permit its use without the fear of super-infection common to most antibiotics which alter the bacterial flora of man" (Goldberg 51, col. 2).

[7] Findings of Fact are abbreviated as "FF".

6. Another advantage of lysostaphin over other antibiotics is its "rapid killing at any stage of growth" (Goldberg 51, col. 2).

Zygmunt

7. Zygmunt reviews a number of studies of the efficacy of lysostaphin in treating established staphylococcal infections in animals, including Goldberg's study, discussed above (Zygmunt 318-324).

8. In another study, 100% of mice infected with an otherwise lethal intraperitoneal staphylococcal infection survived when treated with a single intravenous dose of lysostaphin, in contrast to 53% survival in mice treated with penicillin G instead (Zygmunt 319).

9. In yet another study, mice with established methicillin-resistant staphylococcal renal abscesses demonstrated the effectiveness of a single dose of lysostaphin followed by daily doses of methycillin on succeeding days, "suggest[ing] that a single exposure to lysostaphin may increase the susceptibility of staphylococci to eventual destruction by methicillin" (Zygmunt 322-323).

10. There are potential risks associated with using lysostaphin to treat established staphylococcal infections in humans, that must be balanced against the potential benefits, as with antimicrobial therapy in general (Zygmunt 326-327, and 330-331).

11. For example, while Zygmunt cautions that "[o]ne should view lysostaphin as a potentially sensitizing protein when administered systemically to man" (Zygmunt 330), he also notes that "no evidence has accumulated thus far that lysostaphin is sensitizing to man" (*id.* at 331), and suggests that "[a] limited course of therapy . . . may involve only marginal

risk" (*id.* at 330). Zygmunt further notes that "[a]lthough in vitro resistance to lysostaphin can be observed frequently in the laboratory [ ], this phenomenon has not been a problem in the *in vivo* situation" (*id.* at 325), and "no strains of staphylococci naturally resistant to lysostaphin have been detected in more than 1,000 human clinical isolates of [ ] staphylococci tested" (*id.*).

12. While Zygmunt concludes that "the potential for [sensitization to lysostaphin] . . . seems too high to risk in an era when staphylococcal disease appears to be generally well controlled by existing antibiotics" (*id.* at 331), he acknowledges that others of skill in the art "take[ ] the position that lysostaphin should be evaluated systemically in man for severe staphylococcal infections[,]" particularly in light of "the increasing number of reports that have appeared in recent years on the occurrence of methicillin-resistant staphylococci" (Zygmunt 330).

13. In addition, Zygmunt suggests that "lysostaphin could provide a reserve mode of therapy in dire situations" (Zygmunt 330), "[s]ince none of the clinically available antibiotics is able to lyse large numbers of staphylococci regardless of their metabolic state with the effectiveness of lysostaphin" (*id.*), and further suggests that lysostaphin "be tested in those instances of human staphylococcal disease where it is imperative to decrease the number of microorganisms present in infected tissues (endocarditis, infected vascular grafts, atrioventricular shunts, etc.)" (*id.*).

14. Zygmunt also suggests that it could be beneficial to administer lysostaphin in combination with a semisynthetic penicillin (Zygmunt 330). The underlying rationale is that "initial lysostaphin therapy may lower the

titers of staphylococci within established lesions sufficiently to allow conventional antimicrobials to exert a therapeutic effect and to enable the host's defense mechanisms to function more effectively. In addition, the rapid elimination of circulating staphylococci in cases of staphylococcal bacteriemia may prevent metastatic infection" (*id.* at 330-331).

15. With respect to dosage levels in humans, Zygmunt suggests that "short-term intravenous doses to man in the range of 10 mg/kg b.i.d. [i.e., twice a day] of lysostaphin might be expected to cause no serious toxic effects" (Zygmunt 327).

Stark

16. Stark teaches that lysostaphin effectively cleared methicillin-resistant *Staph. aureus* (MRSA) from infected abscesses in a neutropenic patient (Stark 240).

17. "Despite potential immunogenicity, controlled trials of lysostaphin may be indicated now as adjunctive therapy in human staphylococcal infections in which mortality and morbidity remain high, as in overwhelming or resistant involvement of lung, liver, brain, endocardium, and bone by *Staph. aureus*" (Stark 240).

Oldham

18. Recombinant lysostaphin was available prior to the present invention (Oldham 4175), and was effective against *Staph. aureus* (*id.* at 4178).

19. Recombinant lysostaphin "is highly immunogenic when administered to some species parenterally *in adjuvant*" (Oldham 4182, emphasis added).

Dixon

20. "Bacteriocidal antimicrobials, such as methicillin, interrupt active cell wall synthesis. Staphylococci residing in high titers within abscess lesions may be refractory to these antimicrobial agents because of their sluggish metabolism" (Dixon 67).

21. "In contrast, lysostaphin is active against staphylococci in all stages of growth and metabolic activity" (Dixon 67).

22. "By reducing the number of staphylococci in . . . lesions by more than 90 per cent, . . . [lysostaphin] may allow the remaining microorganisms to again become metabolically active and thus more susceptible to the antimicrobial action of methicillin" (Dixon 67-68).

23. Treatment of established renal abscesses "with a single dose of lysostaphin followed by methicillin therapy . . . produced a reduction in microbial titers significantly greater than that achieved by either . . . alone" (Dixon 67).

Miscellaneous

24. A recombinant lysostaphin is a "lysostaphin analogue" whether it has the same sequence as native lysostaphin or a modified sequence, as long as it "retains the . . . [ability] of proteolytic attack against glycine-containing bridges in the cell wall peptidoglycan of staphylococci" (Spec. 6: 15-20).

DISCUSSION

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that is was obvious under § 103." *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1742 (2007).

The principal issue raised by this appeal, then, is whether administering recombinant lysostaphin to humans to treat an established staphylococcal infection would have been obvious at the time of the invention, given the scope and content of the prior art, the level of ordinary skill in the art, and the differences between the claimed invention and the prior art. A related issue is whether administering a second antimicrobial, in combination with lysostaphin, would have been obvious.

We agree with the Examiner that the invention of claims 4, 5, 32, 44-51, 57, and 61-66 would have been obvious over the teachings of Zygmunt, Goldberg, Stark, and Oldham, although for different reasons than those advanced by the Examiner. That is, we find that the references of record

establish that one of skill in this art would have recognized, and been accustomed to weighing, the relative risks and benefits of antimicrobial therapy (FF 11-15). That being the case, we find that administering lysostaphin to humans to treat established staphylococcal infections would have been obvious to one of skill in the art at the time of the invention (and indeed was explicitly suggested by persons of skill in the art (FF 12)), *despite* lysostaphin's potential for immunogenicity (FF 11, 12, 17), given the recognition in the art that staphylococcal infections resistant to conventional antibiotics (e.g., methicillin-resistant *Staph. aureus* (MRSA) infections) are often sensitive to lysostaphin (FF 9, 12, 14, 16, 21), the recognition that it is imperative to rapidly decrease the sheer number of microorganisms present in infected tissues like heart valves and in infections associated with devices like atrioventricular shunts (FF 13), the recognition that "none of the clinically available antibiotics is able to lyse large numbers of staphylococci regardless of their metabolic state with the effectiveness of lysostaphin" (FF 13), and the recognition that lysostaphin is highly selective and can be used without fear of super-infection common to most antibiotics which affect the bacterial flora of humans less-selectively (FF 5).

We further find that short-term intravenous administration of lysostaphin in the range of 10 mg/kg, twice a day - a protocol that meets the requirement of the claims - would have been obvious, given Zygmunt's suggestion that this particular protocol would not be expected to cause adverse reactions in humans (FF 15).

In addition, we agree with the Examiner that it would have been obvious for one of skill in the art to administer recombinant lysostaphin,

rather than native lysostaphin, given the availability of the recombinant product and its comparability to native lysostaphin (FF 18, and Answer 7[8]).

Finally, we agree with the Examiner that the invention of claims 32, 46, 47, 50, 51, 56, 58, and 59 would have been obvious over the teachings of Zygmunt, Goldberg, Stark, Oldham, and Dixon. That is, we agree with the Examiner that it would have been obvious for one of skill in the art to have administered lysostaphin in combination with another antimicrobial agent, given the recognition that lysostaphin acts quickly to kill most, but not necessarily all, of the Staphylococci present in an established lesion, while at the same time, rendering the remaining organisms more susceptible to other, conventional antimicrobials (FF 9, 14, 17, 22, 23, and Answer 8-9).

We have considered Appellants arguments and the Declaration of Dr. Michael Climo,[9] but are not persuaded otherwise, for the reasons discussed below.

Appellants argue that "Goldberg . . . teaches that dosages in the claimed range do not achieve the same result as [ ] higher dosages but, rather, result in an unacceptable increase in resistant strains and eventual relapse of the dogs being treated" (Appeal Br. 5[10]), and "dosages of *up to 25 mg/kg/day* . . . are substantially lower than any dosage administered to a 'well' or 'improved' dog in Goldberg" (*id.* at 9). Appellants also rely on Dr. Climo's assertion that "treatment of experimental canine endocarditis . . .

[8] The Answer referred to here and elsewhere in this opinion is the Supplemental Examiner's Answer mailed October 30, 2006.
[9] Declaration of co-inventor Michael Climo, M.D. (hereinafter "Decl."), dated September 27, 2001, submitted under 37 C.F.R. § 1.132, and resubmitted with the Appeal Brief.
[10] The Appeal Brief referred to here and elsewhere in this opinion is the Third Replacement Appeal Brief filed February 2, 2006.

cannot be extrapolated to treatment of humans. Nor is it predictive of the efficacy of treatment in humans" (Decl. ¶9).

In a similar vein, Appellants argue that Stark's study "involved a single human and is more speculative of treatment in humans than conclusive" (Appeal Br. 7), and does not "teach[ ] or suggest[ ] that lysostaphin is effective as routine bactericide treatment in humans for systemic infection" (Decl. ¶ 10). Appellants also argue that Oldham "is limited to the treatment of a specific staphylococcal infection not found in humans, namely bovine mastitis" (Appeal Br. 8), and "[o]ne of skill in the art would recognize that non-systemic use of recombinant lysostaphin in a non-human model is not predictive of systemic use in humans" (Decl. ¶ 12).

These arguments are not persuasive, particularly as none of the arguments addresses Zygmunt's or Stark's teachings and suggestions regarding the use of lysostaphin in treating staphylococcal infection in humans. The claims are directed to systemic administration of lysostaphin to treat established staphylococcal infections in humans, and the prior art establishes that administration of lysostaphin to humans was specifically contemplated in instances of "established," "overwhelming," or "resistant" staphylococcal infections in humans prior to Appellants' invention (FF 13, 17). Moreover, the claims require administration of lysostaphin in an amount ranging from 0.5 to 30 mg/kg/day, or in an amount up to 25 mg/kg/day. Zygmunt explicitly suggests administering lysostaphin intravenously at a dose encompassed by the claims: 10 mg/kg, twice a day, i.e., 20 mg/kg/day (FF 15).

Finally, with respect to the use of recombinant lysostaphin, Dr. Climo notes that Oldham teaches that "recombinant lysostaphin 'is highly immunogenic when administered to some species parenterally in adjuvant'" (Decl. ¶ 13), and argues that "[o]ne of ordinary skill in the art would instantly recognize, therefore, that such a highly immunogenic protein is eminently unsuitable for systemic use" (*id.*).

This argument is not persuasive. The fact that a protein might be immunogenic when administered with an adjuvant does not necessarily mean that it will be immunogenic when administered without an adjuvant, as would be the case in a treatment protocol. At any rate, as discussed above, Zygmunt notes that "no evidence has accumulated thus far that lysostaphin is sensitizing to man" (Zygmunt 331), and suggests that "[a] limited course of therapy . . . may involve only marginal risk" (*id.* at 330) (FF 11).

CONCLUSION

We affirm the rejection of claims 4, 5, 32, 44-51, 57, and 61-66 under 35 U.S.C. § 103(a) as unpatentable over Zygmunt, Goldberg, Stark and Oldham, and the rejection of claims 32, 46, 47, 50, 51, 56, 58, and 59 under 35 U.S.C. § 103(a) as unpatentable over Zygmunt, Goldberg, Stark, Oldham, and Dixon. Because our reasoning differs from that of the Examiner, however, we designate our affirmances as new grounds of rejection.

TIME PERIOD FOR RESPONSE

This decision contains a new ground of rejection pursuant to 37 C.F.R. § 41.50(b) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12, 2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)). 37 C.F.R. § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 C.F.R. § 41.50(b) also provides that the Appellants, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

> (1) *Reopen prosecution*. Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the Examiner, in which event the proceeding will be remanded to the Examiner. . . .
>
> (2) *Request rehearing*. Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

Should the Appellants elect to prosecute further before the Examiner pursuant to 37 C.F.R. § 41.50(b)(1), in order to preserve the right to seek review under 35 U.S.C. §§ 141 or 145 with respect to the affirmed rejection, the effective date of the affirmance is deferred until conclusion of the prosecution before the Examiner unless, as a mere incident to the limited prosecution, the affirmed rejection is overcome.

If the Appellants elect prosecution before the Examiner and this does not result in allowance of the application, abandonment or a second appeal, this case should be returned to the Board of Patent Appeals and Interferences

for final action on the affirmed rejection, including any timely request for rehearing thereof.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED; 37 C.F.R. § 41.50(b)

Ssc

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